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EXAMINER	
SWITZER, JULIET CAROLINE	

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 01/21/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/085,056	MARUYAMA ET AL.	
	Examiner	Art Unit	
	Juliet C. Switzer	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 October 2004 and 10 November 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14* is/are pending in the application.

4a) Of the above claim(s) *1,2,4,8 and 11-14* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *3,5-7,9 and 10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. *1104*.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submissions filed on 10/27/04 and 11/10/04 have been entered.

2. This action is written in response to applicant's correspondence submitted 10/27/04 and 11/10/04. Claims 3, 4, 5, 6, 7, 8, 9, 11, 12, 13 and 14 have been amended. Claims 1-14 are pending. In view of applicant's election, claims 3, 5, 6, 7, 9, and 10 are examined herein. Applicant's amendments and arguments have been thoroughly reviewed, but are not persuasive for the reasons that follow. Any rejections not reiterated in this action have been withdrawn. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. **This action is FINAL.**

Claim Objections

3. The claim objections were overcome by amendment to the claims.

Claim Rejections - 35 USC § 112

4. The rejection of claims 3, 5, 6, 7, 9, and 10 under 35 U.S.C. 112, second paragraph, as being indefinite is WITHDRAWN in view of the amendments to the claims.

Claim Rejections - 35 USC § 103

5. Claims 3, 9, and 10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bekkaoui *et al.* (US 6136533) in view of all of the following references: Gilgen *et al.* (Research

in Microbiology (1998 Feb) 149(2) 145-154), Calderwood *et al.* (PNAS USA, Vol. 84, p. 4364-4368), and Buck *et al.* (Biotechniques (1999) 27(3):528-536).

The instant method is drawn to a process for detecting verotoxin 1 RNA (VT1 RNA). The basic methodology used in the method provided by Bekkaoui *et al.* Bekkaoui *et al.* teach a process of detecting nucleic acid in a sample, wherein a specific sequence :

synthesizing a cDNA with a RNA-dependent DNA polymerase using a specific sequence of a RNA present in a sample as a template, thereby producing a RNA-DNA double strand (Col. 13, lines 25-34);

digesting the RNA of said RNA-DNA double strand with Ribonuclease H to form a single stranded DNA (Col. 13, lines 34-36);

synthesizing a double stranded DNA having a promoter sequence capable of transcribing said RNA sequence or a RNA comprising a sequence complementary to said RNA sequence with a DNA-dependent DNA polymerase sand said single-stranded DNA as template,

producing a RNA transcription product in the presence of RNA polymerase, and said RNA transcription product is subsequently used as the template for the single stranded DNA production with said RNA-dependent DNA from said double-stranded DNA (Col. 13, lines 36-40).

The method taught by Bekkaoui *et al.* employs a first primer having a sequence homologous to said specific sequence and a second primer having a sequence complementary to said specific sequence, wherein either the second primer has a sequence having an RNA polymerase promoter added at its 5'-region (Col. 13, lines 15-17).

Bekkaoui *et al.* suggest that suitable target nucleic to be used with their disclosed methodologies include nucleic acid molecules obtained from "viruses, prokaryotes, or eukaryotes (Col. 5, lines 66-67)." Bekkaoui *et al.* further teach their methods have advantages over other nucleic acid technologies, for example PCR, because they are simple, rapid and inexpensive to use, and unlike other amplification technologies (like PCR) can be accomplished at a relatively constant temperature (Col. 2, lines 15-20)." Bekkaoui *et al.* do not teach a method for detecting VT1 RNA in particular, and further do not teach a method wherein a primer comprising 10 or more nucleotide from instant SEQ ID NO: 2 or SEQ ID NO: 15 is used. With regard to claims 9 and 10, they do not teach a method wherein the first oligonucleotide consists of SEQ ID NO: 2 or SEQ ID NO: 15.

Gilgen *et al.* exemplify an amplification reaction in which the VT1 gene is utilized as a target (p. 148). Gilgen *et al.* use primers based on the sequence of Calderwood *et al.*

Calderwood *et al.* teach the sequence of the full length VT1 gene from E. coli (Figure 2; referred to by Calderwood *et al.* as SltA). Instant SEQ ID NO: 2 and instant SEQ ID NO: 15 are within the sequence taught by Calderwood *et al.* Instant SEQ ID NO: 2 consists of the complement of nucleotides 776-795 of the sequence taught by Calderwood *et al.* and instant SEQ ID NO: 15 consists of nucleotides 660-684 of the sequence taught by Calderwood *et al.*

Buck *et al.* compare a wide variety of primers from within a single target sequence and demonstrate that primers selected using a variety of methods all function as equivalents. Buck expressly provides evidence of the equivalence of primers. Specifically, Buck invited primer submissions from a number of labs (39) (page 532, column 3), with 69 different primers being submitted (see page 530, column 1). Buck also tested 95 primers spaced at 3 nucleotide intervals

along the entire sequence at issue, thereby testing more than 1/3 of all possible 18 mer primers on the 300 base pair sequence (see page 530, column 1). When Buck tested each of the primers selected by the methods of the different labs, Buck found that EVERY SINGLE PRIMER worked (see page 533, column 1). Only one primer ever failed, No. 8, and that primer functioned when the experiment was repeated. Further, EVERY SINGLE CONTROL PRIMER functioned as well (see page 533, column 1). Buck expressly states "The results of the empirical sequencing analysis were surprising in that nearly all of the primers yielded data of extremely high quality (page 535, column 2)." Therefore, Buck provides direct evidence that all primers would be expected to function, and in particular, all primers selected according to the ordinary criteria, however different, used by 39 different laboratories. It is particularly striking that all 95 control primers functioned, which represent 1/3 of all possible primers in the target region. This clearly shows that every primer would have a reasonable expectation of success.

Therefore, given the general method taught by Bekkaoui *et al.*, the fact that Gilgen *et al.* exemplify that the VT1 gene as a target for amplification and detection, and the sequence of the VT1 gene taught by Calderwood *et al.*, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the modified the taught by Bekkaoui *et al.* so as to have used them for the detection of the VT1 gene. One would have been motivated to use the methods taught by Bekkaoui *et al.* in order to take advantage of the methodology as taught by Bekkaoui *et al.*, who state that the method can be carried out "in the presence of heterologous nucleic acid molecules, at a relatively constant temperature and without serial addition of reagents (Col. 13, lines 1-13)." One would have been motivated to detect the VT1 gene because it was a known target useful for the detection of toxigenic E. coli in a sample.

With regard to the selection of primers, one would have been motivated to select any primers from within the VT1 gene as taught by Calderwood *et al.* for the detection of the gene in the methods taught by Bekkaoui *et al.*, as each of these primers would be expected to function as functional equivalents of one another for the detection of the VT1 gene, including primers which comprise at least 10 contiguous nucleotides of SEQ ID NO: 2 and SEQ ID NO: 15 or primers which consist of SEQ ID NO: 2 and SEQ ID NO: 15. In the absence of a secondary consideration, such as unexpected results, the invention is *prima facie* obvious.

6. Claims 5, 6, and 7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bekkaoui *et al.* (US 6136533) in view of all of the following references: Gilgen *et al.* (Research in Microbiology (1998 Feb) 149(2) 145-154), Calderwood *et al.* (PNAS USA, Vol. 84, p. 4364-4368), and Buck *et al.* (Buck et al (Biotechniques (1999) 27(3):528-536) as applied to 3 above, and further in view of Ishiguro *et al.* (Nucleic Acids Research, 1996, Vol. 24, No. 24, pages 4992-4997).

The teachings of Bekkaoui *et al.* in view of Gilgen *et al.*, Calderwood *et al.* and Buck *et al.* are applied to claims 5, 6, and 7 as they are applied in the previous rejection.

With regard to claim 5, these together do not provide a method wherein said amplification is carried out in the presence of an oligonucleotide probe labeled with an intercalator fluorescent dye wherein the probe is complementary to the RNA transcription product and wherein the binding of the probe to said RNA transcription product results in a change of the fluorescent property relative to that of a situation where a complex formation is absent, then measuring the fluorescence intensity of the reaction solution. With regard to claim

6, therefore, these do no teach that the probe is complementary to at least a portion of the sequence of the RNA transcription product, nor do these combined specifically teach the sequence of the probe as being at least 10 contiguous bases of SEQ ID NO: 24 (as recited in claim 7).

Ishiguro *et al.* teach methods wherein a probe labeled with an intercalator fluorescent dye is included in an *in vitro* transcription application in order to provide an easy and specific homogeneous method to detect a nucleic acid sequence (p. 4992). With regard to claim 6, the probe used by Ishiguro *et al.* is designed to be complementary to a portion of the RNA transcription product, and the fluorescent property changes when the probe is bound (p. 4992 and 4994, first column). Ishiguro *et al.* teach that "The present success of the applicability of the probe to real-time monitoring of the in vitro transcription showed that YO-linked DNA probe can be a powerful tool with which to construct a new methodology to study the dynamics of gene expression, and also to provide a more practical way of detecting and quantifying a target sequence in a clinical specimen specifically in a homogeneous format (p. 4997)." Thus, in light of the teachings of Ishiguro *et al.*, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have included an oligonucleotide probe labeled with an intercalator fluorescent dye wherein the probe is complementary to the RNA transcription product in the method taught by Bekkaoui *et al.* in view of Gilgen *et al.*, Calderwood *et al.* and Buck *et al.* The ordinary practitioner would have been motivated to include such a probe in order to provide a practical way of detecting and quantifying target sequence in a clinical specimen in a homogeneous format, as is taught by Ishiguro *et al.*

With regard to claim 7, instant SEQ ID NO: 24 consists of the complement of nucleotides 730-751 of the sequence taught by Calderwood *et al.* Given the combined teachings of Bekkaoui *et al.* in view of Gilgen *et al.*, Calderwood *et al.*, and Buck *et al.* and further in view of Ishiguro *et al.*, it would have further been prima facie obvious to one of ordinary skill in the art to have selected a probe from within the sequence taught by Calderwood *et al.* to have used for detection of the isothermal amplification product. One would have been motivated to select any probe within the selected primers, as all probes, like the primers, would be expected to function as equivalents.

Response to Remarks

The only remaining rejections are those under 103.

Applicant argues that the oligonucleotides "disclosed by the present specification" provide superior RNA amplification results compared to all other oligonucleotides, and on this basis disagrees that all oligonucleotides are equivalents. In support of this argument applicants point to figure 3 as showing "surprising and superior RNA amplification results provided by" the primer combination SEQ ID NO: 2 and SEQ ID NO: 15, referring to Figure 3 for support of this argument. This is not persuasive for a number of reasons. Figure 3 shows the result of amplification reactions using three different primer pairs, three different reactions for each of the pairs. All three primer pairs amplified the target RNA with the same sensitivity. That is, all three pairs amplified the target RNA at both 10^3 and 10^4 copies/ 30 µl. The instant claims are drawn to a process for detecting the VT1 RNA, and this example appears to show what the rejection argues, that is, the primer pairs are equivalent with respect to their ability to detect the target. That is, they all detected the target. Detection, in the claim, is a yes or no issue. The

claims do not recite any quantitative step, and therefore, the darkness of the band does is not relevant with regard to the question of whether or not detection occurs. The text of the specification states that "Since specific bands were confirmed in any of the combinations shown in Table 3, it was demonstrated that these oligonucleotides are effective in detecting VT1 RNA (p. 21, lines 15-18)." This statement seems to imply that any of the sets of primer/probe combinations in Table 3 can be used to effectively detect VT1 RNA in an equivalent manner. Thus, the unexpected result suggested by Applicant is not clear. Arguments of counsel are not found to be persuasive in the absence of a factual showing. MPEP 716.01(c) makes clear that

> "The arguments of counsel cannot take the place of evidence in the record. In re Schulze , 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965). Examples of attorney statements which are not evidence and which must be supported by an appropriate affidavit or declaration include statements regarding unexpected results, commercial success, solution of a long - felt need, inoperability of the prior art, invention before the date of the reference, and allegations that the author(s) of the prior art derived the disclosed subject matter from the applicant."

Applicant argues that the superior amount and clarity of banding provided by selecting primers consisting of SEQ ID NO: 2 and SEQ ID NO: 15 (plus the RNA polymerase binding site) is clear from inspection of Figure 3. Inspecting figure 3, it is agreed that the banding is clearer for this primer pair, however, the assay gel itself is not a quantitative tool, and there is no actual quantitative data regarding the amount of DNA amplified. The difference in banding could be an artifact of binding to the dye, for example or could represent different well to well variation in amplification reactions. Regardless, as previously discussed, even if there is more amplification product for one pair, this does not appear to affect the outcome with regard to whether or not the primer pairs "detect" the sample. Applicant seems to imply that darker bands are a superior means for detection, however, all of the primer pairs exemplify seem to provide an

equivalent result with regard to the question of whether or not detection occurs. All primer pairs tested detect with the same sensitivity.

Finally, applicant on page 13 of the response, extends the argument to non-elected primer/probe pairs, stating that they "provide superior results compared to selection of oligonucleotides which are excluded from the scope of the invention (p. 13, third paragraph)." These non-elected species have not been considered as the elected species is properly rejected. However, it is noted nonetheless that there is no evidence on the record to support this argument of counsel. Absent a clear showing of evidence, the argument is not persuasive.

Therefore, the 103 rejection is maintained.

Conclusion

7. No claim is allowed.

8. All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period

will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

9. A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Juliet C Switzer whose telephone number is (571) 272-0753. The examiner can normally be reached on Monday through Friday, from 9:00 AM until 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary ~~Benzion~~ Jones can be reached by calling (571) 272-~~0782.~~ 0745.

The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571)272-0507.

Juliet C. Switzer

Juliet C Switzer
Examiner
Art Unit 1634

January 12, 2005